Direct Drug Delivery to the CNS

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Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury

Joseph T. Giacino, Ph.D. et.al.  n engl j med 366;9  nejm.org march 1, 2012
30 Years Experience with CNS Drug Delivery
First Patient Intrathecal Baclofen 1984
Why IT Delivery Works

Avoids the blood brain barriers

High local spinal concentration
Key to Understanding Intrathecal Delivery

REGIONAL DISTRIBUTION

VERY SLOW KINETICS OF DISTRIBUTION

WIDE RANGE OF DOSING
Bolus Distribution over Time

![Diagram showing bolus distribution over time with water soluble and bolus markers.](image)
The concentration distribution depends on the catheter site.
The Distribution of Medication along the Spinal Canal after Chronic Intrathecal Administration.

Figure 1. 111In-DTPA images of lower (left) and upper (right) spinal column taken 72 hours after the start of a slow intrathecal infusion of the radionuclide with an implantable pump system.
Figure 2. Decline of $^{111}$In-DTPA concentration as the compound ascends the thoracic spinal column after slow intrathecal infusion. The 0-cm point is at the T12 vertebrae and the 20-cm point is at the T2 vertebrae. The percentage of maximum concentration is the ratio of counts at points along the spinal canal to the level measured at T12. Data are presented as mean +/- standard deviation for four patients.
Fig. 5 Average bupivacaine concentration in anterior and posterior spinal cord specimens from the bolus group (A). Bupivacaine concentration differed significantly between the anterior and posterior halves of the spinal cord and as a function of distance from the site of administration. Average baclofen concentration in anterior and posterior spinal cord specimens from the bolus group (B). Baclofen concentration differed significantly as a function of distance from the site of administration but did not differ between the anterior and posterior halves of the spinal cord.

Cerebrospinal Fluid and Spinal Cord Distribution of Baclofen and Bupivacaine during Slow Intrathecal Infusion in Pigs.
Bernards, Christopher
Distribution from Lumbar Infusion to the Brain

- Baclofen
- Morphine
- BDNF
- CNTF

  Water soluble
  Convective Flow
  Low uptake by spinal cord and dura
WHY DOES DRUG DISTRIBUTE ALONG THE SPINAL CORD?

TURNOVER OF CSF
MIXING DUE TO CSF PULSATIONS
CSF Flow

Total CSF  130 ml
Turnover  500 ml
Exit Sites
IF THE CONCENTRATION IN THE LUMBAR CSF IS DETERMINED BY THE OVERALL CSF TURNOVER

Total CSF 125-150 ml
Rate of CSF production 0.3cc/minute or 450 cc/day
Then a several hour ½ life is reasonable if there is good mixing in the CSF compartments
Model for testing CSF dynamics
Effect of pulsations on distribution
STAGNANT VS PULSATILE

(a) Stagnant flow 
\[ t = 3 \text{ minutes} \]
- Experiment
- Simulation

(b) Pulsatile flow 
\[ t = 3 \text{ minutes} \]
- Experiment
- Simulation

Normalized species concentration vs. Distance, m
PREDICTED DISTRIBUTION WITH PULSATILE FLOW
Time course of reduction of spasticity from a bolus IT baclofen
Pain score vs spinal CSF concentration of morphine
Location of the GABA-B receptors in the rodent spinal cord
Target of baclofen in the human spinal cord
Diffusion in the Extracellular Space
Tortuosity

(a) geometry
(b) dead space
(c) obstruction
(d) binding
(e) charge
Large variation in dose needed to control spasticity
Why is there such a wide range of dosing?

- Catheter placement
- Size and configuration of the spinal canal
- Flow pattern of the CSF
- CSF pulsations
- Turbulence due arachnoid, nerve roots, dentate ligaments
- Pathology: cysts, tumor, etc
Bolus vs Constant Infusion

• Distribution is different

• Penetration into tissue varies

• Resident time in tissue depends on each specific molecule

• Location of the catheter determines distribution

• Local factors effecting flow mean great individual differences in distribution
Calculations suggest the only 5% of the infused morphine goes into the spinal cord where it has its primary effect so 95% goes to the brain subarachnoid space
STUDIES OF CEREBROSPINAL FLUID FLOW AND PENETRATION INTO BRAIN FOLLOWING LATERAL VENTRICLE AND CISTERNA MAGNA INJECTIONS OF THE TRACER [14C]INULIN IN RAT

M. G. PROESCHOLDT, B. HUTTO, L. S. BRADY and M. HERKENHAM*
Section on Functional Neuroanatomy, National Institute of Mental Health, Building 36, Room 2D-15, Bethesda, MD 20892, U.S.A.

*Neuroscience Vol. 95, No. 2, pp. 577–592, 2000
Hunter syndrome, also known as mucopolysaccharidosis Type II (MPS II), is a lysosomal storage disease caused by a deficient (or absent) enzyme, iduronate-2-sulfatase (I2S).

- Idursulfase works IV for Hunter’s syndrome
- No effect on the CNS disease
- IT trial intermittent lumbar bolus injection primate trial
Shire HGT
Nonclinical Development
    Teresa Wright
    Brian Felice
    Richard Pfeifer
    Perry Calias
    Jing Pan
    Anne Renee Graham
    Charlene Neal
    Kate Zaleski
    Nancy Savioli

Northern Biomedical Research
    Randy Reed
    Jill Zeller
    Robert Boyd
6-month toxicity study in cynomolgus monkeys with monthly IT dosing and weekly IV dosing

<table>
<thead>
<tr>
<th>IT dose (mg)</th>
<th>IV dose (mg/kg)</th>
<th>No. of males</th>
<th>Treatment</th>
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<td>Device control (PBS)</td>
<td>Device control (saline)</td>
<td>6</td>
<td>IT treatment monthly (6 doses)</td>
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<tr>
<td>vehicle</td>
<td>vehicle</td>
<td>12</td>
<td>IV treatment weekly (23 doses)</td>
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<tr>
<td>3</td>
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<td>12</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.5</td>
<td>6</td>
<td>Sacrifice at 6 months &amp; 1 month recovery</td>
</tr>
<tr>
<td>100</td>
<td>0.5</td>
<td>12</td>
<td></td>
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</tbody>
</table>
Biodistribution analysis by IHC and enzyme activity

- Brain, spinal cord and liver sections taken

3 mm coronal slices taken using a brain matrix; alternating slices used for histopathology, IHC and enzyme activity
Dose-dependent idursulfase activity in brain slices

![Graph showing dose-dependent idursulfase activity in brain slices. The x-axis represents brain slice time points (0 to 21), and the y-axis represents mean I2S activity (nmol/hr/mg protein). Different lines represent various conditions: DC, Vehicle, Vehicle-REC, 3 mg/IT Injection, 3 mg/IT Injection-REC, 30 mg/IT Injection, 100 mg/IT Injection, 100 mg/IT Injection-REC. The graph illustrates the trend of idursulfase activity across different conditions and time points.](image-url)
Highest intensity of idursulfase-staining in meninges

Cerebrum; 3 mg; 20X.

Cerebrum; 30 mg; 20X.

N = Neurons; G = Glial cells; M = Meningeal Cells

To be as brave as the people we help
Idursulfase-staining intensity and penetration increased with dose

N = Neurons; G = Glial cells; M = Meningeal Cells; P = epi/peri/endoneurium

Cerebrum; 100 mg; 40X.

Lumbar spinal cord; 100 mg; 20X.

To be as brave as the people we help
Pharmacokinetics And Tolerability Of An Antisense Oligonucleotide Administered As An Intrathecal Lumbar Bolus Injection In Monkey

Robert A. Fey, Daniel A. Norris, J.R. Zeller, R.B. Boyd, Scott P Henry
Isis Pharmaceuticals, Inc., Carlsbad, CA
Northern Biomedical Research, Muskegon, MI
1.5 mg. lumbar bolus

spinal cord

brain
Tissue levels with constant infusion
Intraventricular Infusion for Alzheimer's Disease
Octreotide

(D)Phe—Cys—Phe

S

S

(D)Trp

Lys

Thr—ol—Cys—Thr

Ala—Gly—Cys—Lys—Asn—Phe—Phe

S

S

Trp

Lys

Cys—Ser—Thr—Phe—Thr

Somatostatin
OCTREOTIDE

Stable in brain tissue
Chronic infusion able to increase the level to two times the normal level of somatostatin in brain tissue
but it did not work clinically
Bethanechol, a cholinergic agonist, did work
Local Delivery into Brain Tissue
Parkinson’s Disease
Parkinson’s Disease vs Normal

Nigra
Loss of dopamine over time vs symptoms

Dopamine in % of control

Adaptive capacity

Compensation = no symptoms

Decompensation

mild symptoms

marked
Cortical-Striatal-Thalamic Motor Pathways

- SMA
- PMC
- Putamen
- Vlo
- VApc
- CM
- Gpe
- GPI
- STN

- Arm
- Face
- Leg
Normal

Dopamine

Direct pathway facilitates movement
Indirect pathway inhibits movement

From SNC

Putamen

Thalamus

Pedunculo-pontine nucleus

Spinal cord
Parkinson’s disease

Diagram showing the neural pathways involved in Parkinson's disease, including the Thalamus, Putamen, Spinal cord, and various nuclei such as GPi, GPe, and STN.
Parkinson patient
Infusion = 100 ng/h

Muscimol concentration (ng/mg protein)

A-P distance from cannula tip (mm)
Microelectrode recording of neuronal activity during the microinjection of lidocaine in Patient A. Lidocaine was injected at the volumes (μL, bold numbers in grey boxes) and times indicated by the grey boxes to the left side of vertical timeline.

L-DOPA is very good symptomatic treatment but does not change the course of the disease

Deep Brain Stimulation does not change the course of the disease

So

A disease modifying approach is needed
GDNF Delivery For Parkinson’s Disease
GDNF and NRTN are neurotrophic growth factors with the potential to cure Parkinson’s patients

Glial cell line-Derived Neurotrophic Factor (GDNF) supports the survival of dopaminergic neurons *in vitro*, and has since its discovery in 1993 been a strong candidate as a factor that could restore the degenerating dopaminergic neurons *in vivo*. GDNF has reached Phase 2 clinical trials of Parkinson’s disease.

Also gene therapy with neurturin (NRTN), a close homologue of GDNF gives modest hope in Phase 2 clinical trials of Parkinson’s disease but the results need to be improved. Autopsy on two patients showed that NRTN had diffused poorly in the brain.

Four homologous ligands signal through the same receptor tyrosine kinase RET

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*Trupp et al., Arumäe, Saarma, Nature, 1996*
BRISTOL 24 MONTH RESULTS
GDNF – $^{18}$F-dopa PET Changes

![Graph showing PET changes over time for different patients and regions.](image_url)

- **Peri-Catheter Region of Interest**
- **Posterior Putamen**

- **Influx Constant (x1000/min)**
  - Baseline
  - 24-months
  - 6-mon post switch-off

- **Patient 3**
- **Patient 4**
- **Patient 5**
- **Group Mean**
GDNF HISTOLOGY AFTER 43 MONTHS INFUSION

LEFT PUTAMEN  GFAP

RIGHT PUTAMEN  GFAP

LEFT PUTAMEN  TH

RIGHT PUTAMEN  TH

e  f  g  h
Randomized Controlled Trial of Intraputamenal Glial Cell Line–Derived Neurotrophic Factor Infusion in Parkinson Disease
Ann Neurol 2006;59:459–466
For intraparenchymal delivery need:

- Better Neurotrophins
- Better Catheter Systems
- Better Placement
- Better Infusion Protocols
GDNF and NRTN are the only growth factors in clinical trial for chronic neurological disease - different strategies are used to deliver GDNF or NRTN to the Parkinson patient’s brain.
NEUROTROPHIN DEVELOPMENT FOR PARKINSON’S DISEASE

Protein delivery
- GDNF: Biovail/Medgenesis/Fox Pre clinical
- CDNF: Hermo/Fox Pre clinical
- GDNF Variant: Lilly/Medtronic Pre clinical

Viral delivery
- GDNF: NIH Phase I/II
- NRTN: Ceregene/Fox Phase II b
- CDNF: Hermo Pre clinical

Stem cell stimulation
- PDGF: Neuronova/Medtronic Pre clinical
Lentiviral Delivery of NTN
**NRTN gives hope in Phase 2 clinical trials, but the result needs to be improved**

Ceregene Inc.
Press release, 27th of May, 2009

“The company previously announced that the Phase 2 trial did not meet its primary endpoint of improvement in the Unified Parkinson’s Disease Rating Scale (UPDRS) motor off score at 12 months of follow-up, although several secondary endpoints suggested a modest clinical benefit.

The additional, protocol-prescribed analyses reported today focused on further analyses of the data from the 30 subjects who continued to be evaluated under double-blind conditions for up to **18 months which indicate increasing effects of CERE-120 over time.**

**Autopsy on two patients showed that NRTN had diffused poorly in the brain. Therefore better diffusing NRTN variants might give improved results.**

Hamilton et al., Experimental Neurol., 2001

CED of trophic factors of the GDNF family with and without heparin. 5 mg of trophic factor in 5 ml of infusate infused at 0.2 ml/min. Animals were sacrificed immediately. Immunohistochemical staining was performed with antibodies to the respective trophic factor.
Binding to heparin receptors

GDNF

GDNF + Heparin
NRTN specifically binds to GFRα2 and activates RET. NRTN can also activate RET via GFRα2.
Design of new NRTN variants

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<tr>
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<th>Sequence</th>
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<tr>
<td>WT</td>
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<tr>
<td>N1</td>
<td>ALRQARLRRRER</td>
</tr>
<tr>
<td>N2</td>
<td>RRLAQRRRLRAEA</td>
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<td>ALAQRALRAER</td>
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<tr>
<td>N4</td>
<td>ARLQGQGALVGR</td>
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</tbody>
</table>

AR↓LGARPCGL RELEVRVSEL GLGYASDETV LFRYCA GACE AAARVYDGL

RRLRQRRRLR RERVRAQPCC RPTAYEDEV VHEL SARECA CV
Diffusion of Neurotrophic Factors

Commercial
*E. coli* GDNF
Anti-
°©-GDNF

Mammalian
NRTN N2
Anti-°©-NRTN

Commercial
*E. coli* NRTN
WT
Anti-
°©-NRTN

Mammalian
NRTN N4
Anti-°©-NRTN
Initial screening of unpurified NRTN variants: activity & binding to heparin
N2 and N4 do not bind to the cell surface and have an increased spreading in the tissue.
Purified N2 and N4 are active in a rat 6-OHDA Parkinson’s disease model

- 6-OHDA selectively destroys the dopaminergic nigrostriatal pathway (including presynaptic DA-neurons in the striatum):
  - Causes supersensitivity of the postsynaptic dopamine receptors in the striatum.
  - An imbalance in DA activity between two striata causes rotational asymmetry.
  - Rats turn away from the bigger DA content
Ongoing

• Testing of N2 and N4 in a rat 6-OHDA Parkinson’s disease model.
• Testing of N2 and N4 in a rhesus monkey MPTP Parkinson’s disease model (2 x 6 animals)
• Mode of action: retrograde transport and stability of the new NRTN variants.
DBS and Emotions
ventral medial placement of the electrode
The first region of the brain to be targeted with DBS in patients with treatment-resistant depression (TRD) was the subcallosal cingulate (SCC), the ventral-most segment of the cingulate gyrus.
Unique aspects of intrathecal and intraparenchyma delivery of drugs for local, regional and total CNS distribution

- CSF flow
- Convection
- Diffusion

Clinical Results